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ORALLY ADMINISTERED CONTROLLED DELIVERY SYSTEM FOR ONCE DAILY ADMINISTRATION OF CIPROFLOXACIN

Abstract:

A once daily tablet formulation for oral administration in humans for the controlled release of ciprofloxacin comprising a pharmaceutically effective amount of ciprofloxacin, from about 0.1 % to about 8.0 % of a viscolyzing agent and/or a gelling agent, about 5.0% to about 15 % of a gas generating agent, and about 3.0 % to about 15 % of a swelling agent, said percentages being w/w of the composition.

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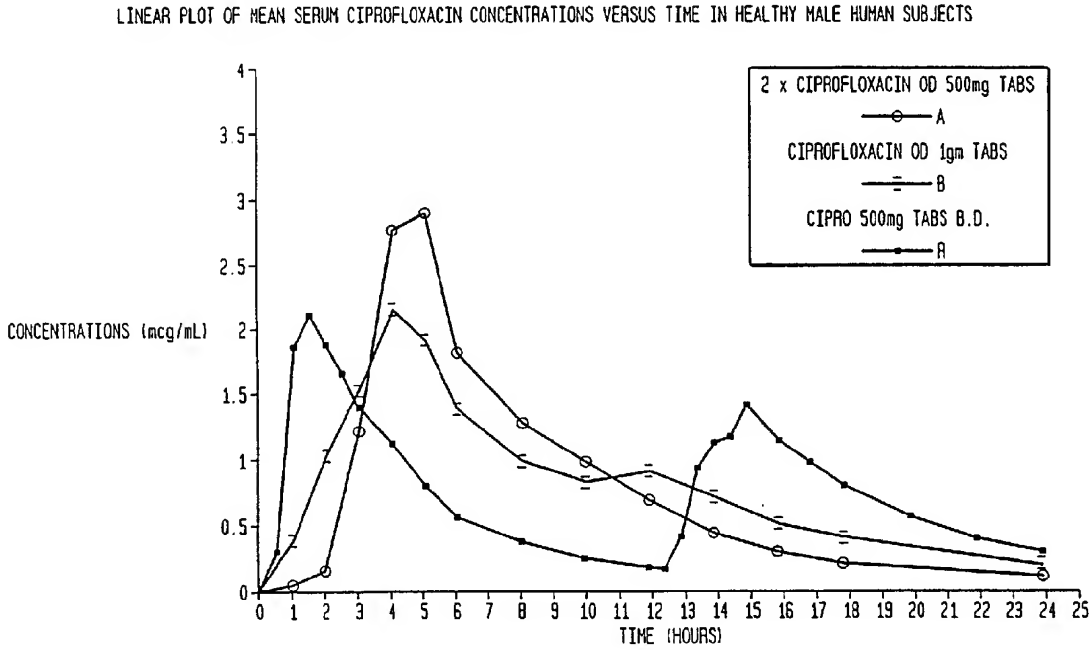

(57) Abstract: A once daily tablet formulation for oral administration in humans for the controlled release of ciprofloxacin comprising a pharmaceutically effective amount of ciprofloxacin, from about 0.1 % to about 8.0 % of a viscolyzing agent and/or a gelling agent, about 5.0% to about 15 % of a gas generating agent, and about 3.0 % to about 15 % of a swelling agent, said percentages being w/w of the composition.

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ORALLY ADMINISTERED CONTROLLED DELIVERY SYSTEM FOR ONCE DAILY ADMINISTRATION OF CIPROFLOXACIN

BACKGROUND OF THE INVENTION

The present invention relates to a pharmaceutical composition in the form of tablets or capsules which provides a combination of spatial and temporal control of drug delivery, specifically for the drug ciprofloxacin, to a patient for effective therapeutic results. The pharmaceutical composition comprises ciprofloxacin, a gas generating component, a swelling agent, and at least one of either a viscolyzing agent and a gelling agent. The swelling agent belongs to a class of highly absorbent compounds commonly referred to as superdisintegrants. This class of compounds includes, for example, cross-linked polyvinyl pyrrolidone and cross-linked sodium carboxymethylcellulose. The viscolyzing agent is a highly viscous material which upon contact with gastric fluid entraps the gas produced by the gas generating component. The viscolyzing agent comprises, for example, a carbohydrate gum, *e.g.*, xanthan gum or a cellulose ether, *e.g.*, hydroxypropyl methylcellulose (methocel). The gelling agent is preferably a cross-linkable gelling agent, such as a water soluble salt of one or more polyuronic acids, *e.g.*, sodium alginate.

The improved controlled drug delivery system of the present invention is designed to deliver effectively ciprofloxacin to a patient over a specific time period (temporal control) and from a particular portion of the patient's gastrointestinal tract (spatial control). The improved controlled drug delivery system avoids dose dumping and results in the most therapeutic administration of ciprofloxacin to a person.

It is well known to those skilled in the art that for ailments requiring multiple doses of a particular drug, the blood levels of a drug need to be maintained above its minimum effective level and below its minimum toxic level in order to obtain the desired therapeutic effects, to avoid undesired toxic effects, and to minimize side effects. When the blood levels of a drug are in this range, the drug is eliminated from the body at a particular rate. A controlled drug delivery system is usually designed to deliver the drug at this particular rate; safe and effective blood levels are maintained for a period as long as the system continues to deliver the drug at this rate. Controlled drug delivery usually results in substantially constant blood levels of the active ingredient as compared to the uncontrolled fluctuations observed when multiple doses of quick releasing conventional dosage forms are administered to a patient. Controlled drug delivery results in optimum therapy, and not only reduces the frequency of dosing, but may also reduce the severity and frequency of side effects.

The above basic concepts of controlled drug delivery are well known to those skilled in the art. Considerable efforts have been made in the last decades to develop new pharmaceutically viable and therapeutically effective controlled drug delivery systems. Attention has been focused particularly on orally administered controlled drug delivery systems because of the ease of administration via the oral route as well as the ease and economy of manufacture of oral dosage forms such as tablets and capsules. A number of different oral controlled drug delivery systems based on different release mechanisms have been developed. These oral controlled drug delivery systems are based on different modes of operation and have been variously named, for

example, as dissolution controlled systems, diffusion controlled systems, ion-exchange resins, osmotically controlled systems, erodible matrix systems, pH-independent formulations, swelling controlled systems, and the like.

An orally administered controlled drug delivery system encounters a wide range of highly variable conditions, such as pH, agitation intensity, and composition of the gastrointestinal fluids as it passes down the gastrointestinal tract. Ideally, an oral controlled drug delivery system will deliver the drug at a constant and reproducible rate in spite of the varying conditions. Considerable efforts have therefore been made to design oral controlled drug delivery systems that overcome these drawbacks and deliver the drug at a constant rate as it passes down the gastrointestinal tract.

It is well known to those skilled in the art that a drug may not be absorbed uniformly over the length of the gastrointestinal tract, and that drug absorption from the colon is usually erratic and inefficient. Also, certain drugs are absorbed only from the stomach or the upper parts of the small intestine. Furthermore, an important factor which may adversely affect the performance of an oral controlled drug delivery system is that the dosage form may be rapidly transported from more absorptive upper regions of the intestine to lower regions where the drug is less well absorbed. Therefore, in instances where the drug is not absorbed uniformly over the gastrointestinal tract, the rate of drug absorption may not be constant in spite of the drug delivery system delivering the drug at a constant rate into the gastrointestinal fluids. More particularly, in instances where a drug has a clear cut "absorption window," *i.e.*, the drug is absorbed only from specific regions of the stomach or upper parts of the small intestine, it may

not be completely absorbed when administered in the form of a typical oral controlled drug delivery system. It is apparent that for a drug having such an "absorption window," an effective oral controlled drug delivery system should be designed not only to deliver the drug at a controlled rate, but also to retain the drug in the upper parts of the gastrointestinal tract for a long period of time.

U.S. Patent No. 5,651,985, assigned to Bayer AG, discloses a composition comprising a pharmacologically active compound, a pharmaceutically acceptable auxiliary, polyvinylpyrrolidone, and a methacrylic acid polymer having an acidic number between 100 and 1200 mg of KOH/g of polymer solid substance. Optionally, the composition also comprises a gas forming additive. The composition absorbs many times its weight of acidic water and forms a highly swollen gel of high mechanical and dimensional stability. The gel forming agent should be sufficient so that after administration it can swell up to a size which prevents passage through the pylorous for a relatively long time. At least 30% by weight and up to 90% by weight of the composition comprises the polymers, and thus dosage forms containing a high dose medicament would be large and inconvenient for oral administration.

Generally, in the field of controlled drug delivery systems, it is known that in order to make a particular drug available as a once-daily tablet or capsule, it is necessary to experiment and invent with the particular drug together with specific excipients. Thus, what particular excipients and in what particular relative amounts may work for a particular active ingredient or drug, to make it available on a once-daily basis, will likely not work for another drug.

Nishioka *et al.* (JP 06024959) is a Japanese patent publication wherein an attempt is made to cause the release of ciprofloxacin over a longer period of time by causing the tablet containing ciprofloxacin to remain suspended in the stomach. The release period obtained by the Nishioka tablet is so slow that only 46% of the Nishioka tablet is dissolved after 24 hours (see plot). The practical and significant effect of this slow dissolution is that the Nishioka formulation would not be effective as a "once daily" ciprofloxacin formulation.

Accordingly, none of the oral controlled drug delivery systems heretofore described is completely satisfactory for the purpose of providing a once daily formulation for the controlled release of ciprofloxacin.

OBJECTS OF THE PRESENT INVENTION

It is an object of the present invention to provide a pharmaceutical composition in the form of tablets or capsules which constitutes a once daily formulation for the controlled release of ciprofloxacin that:

a. generates and entraps a gas in a hydrated matrix upon contact with an aqueous medium or gastric fluids, and which retains a substantially monolithic form in the stomach,

b. provides increased gastric residence and thereby a longer period of residence of the drug delivery system in the gastrointestinal tract,

c. delivers the drug at a controlled rate such that the drug is delivered over a period of time which is the same as or less than the period

of residence of the delivery system in the absorptive regions of the gastrointestinal tract, and

d. provides, as compared to other oral controlled drug delivery systems, increased absorption of a drug that is absorbed largely from the upper parts of the gastrointestinal tract.

It is also an object of the present invention to provide a once daily formulation for the controlled release of ciprofloxacin that maintains its physical integrity, *i.e.*, remains intact or substantially gains a monolithic form when contacted with an aqueous medium, even when the quantity of medicaments is large, and wherein the proportion of polymers is small compared to other components of the system. It is a further object of the present invention to provide a once daily formulation for the controlled release of ciprofloxacin that incorporates a high dose medicament without the loss of any of its desirable attributes, as listed above, such that the system is of an acceptable size for oral administration.

SUMMARY OF THE INVENTION

The present invention provides a novel pharmaceutical composition in the form of tablets or capsules which composition constitutes an orally administered once daily formulation for the controlled release of ciprofloxacin. The pharmaceutical composition comprises ciprofloxacin, a gas generating component, a swelling agent (*e.g.*, cross-linked polyvinylpyrrolidone or cross-linked sodium carboxymethylcellulose), at least one of either a viscolyzing agent (*e.g.*, a carbohydrate gum such as xanthan gum or a cellulose ether such as hydroxypropyl methylcellulose), and a gelling agent (*e.g.*, sodium alginate).

Preferably, the inventive oral controlled drug delivery system which is a pharmaceutical composition in the form of tablets or capsules comprises a pharmaceutically effective amount of ciprofloxacin, about 0.1% to about 8% by weight of at least one of a viscolyzing agent and a gelling agent, about 5% to about 15% by weight of the gas generating component, and about 3% to about 15% by weight of the swelling agent.

More preferably, the amount of at least one of the viscolyzing agent and the gelling agent ranges from about 0.2% to about 5% and the amount of the swelling agent ranges from about 3% to about 15%.

Even more preferably, the present invention is related to a once-daily tablet formulation for oral administration in humans for the controlled release of ciprofloxacin comprising a pharmaceutically effective amount of ciprofloxacin, about 0.2% to about 0.5% sodium alginate, about 0.5 to about 2.0% xanthan gum, about 10.0% to about 25% sodium bicarbonate, and about 5.0% to about 20% cross-linked polyvinylpyrrolidone, said percentages being w/w of the composition, wherein the weight ratio of sodium alginate to xanthan gum is between about 1:1 to about 1:10.

The swelling agents used herein (cross-linked polyvinylpyrrolidone or cross-linked sodium carboxymethylcellulose) belong to a class of compounds known as super-disintegrants which usually function to promote disintegration of a tablet by absorbing large amounts of water and thereby swelling. This expansion, as well as hydrostatic pressure, cause the tablet to burst. In a tablet which also comprises a gas generating component (which may actually be a gas

generating couple), one would expect the tablet to disintegrate instantly upon contact with aqueous fluid, if not blow apart. Remarkably, it has been found that in the presence of an instantly acting viscolyzing agent and/or a gelling agent, the generated gas is entrapped and the super-disintegrant acts as a swelling agent which swells to, preferably, at least twice its original volume. Thus, the combination of the gas generating component, the swelling agent which is actually a super-disintegrant, and the viscolyzing agent or a gelling agent permit the formulation to act as a controlled drug delivery system. Additionally, with the passage of time, the gelling agent and/or the viscolyzing agent produces a cross-linked three-dimensional molecular network resulting in a hydrodynamically balanced system that is retained in the stomach and releases the drug over a sustained period of time.

Surprisingly, it has been found that a tablet or capsule formed from the formulation of the present invention is retained for longer periods of time in the stomach (spatial control) than previously known hydrophilic matrix tablets, floating capsules and bioadhesive tablets when these systems are administered with food. The formulation of the present invention results in release of the drug into the more absorptive regions of the gastrointestinal tract, *i.e.*, into the stomach and the small intestine rather than into the large intestine where drug absorption is poor or erratic. Thus, one may expect that if the drug is released at a constant and controlled rate, it will also be absorbed at a more or less constant rate.

Even more surprisingly, it has been found that even for a drug that is absorbed only from the upper gastrointestinal tract (*i.e.*, from the stomach down

to the jejunum), such as ciprofloxacin, the present formulation provides the desired absorption at a rate such that effective plasma levels are maintained for a prolonged duration and the formulation is especially suitable for once-daily administration (temporal control). Moreover, the formulation provides increased absorption of the drug as compared to other oral controlled drug delivery systems such as hydrophilic matrix tablets and floating capsules. This is achieved by adjusting the time period of release for the drug so that it is about the same as or less than the retention time of the tablets at the site of absorption. Thus, the tablet or capsule is not transported past the "absorption window" prior to releasing all of the drug, and maximum bioavailability is attained.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a graph illustrating mean serum concentration vs. time for the drug ciprofloxacin free base and ciprofloxacin HCl when incorporated in the oral controlled drug delivery system as compared to the presently marketed Cipro™ (Bayer Corp.) immediate release tablets.

Figs. 2 and 3 are graphs illustrating mean plasma concentration vs. time for ciprofloxacin free base when incorporated in the oral controlled drug delivery system of the present invention as compared to Cipro™ immediate release tablets under fed and fasting conditions.

DETAILED DESCRIPTION OF THE INVENTION

According to the present invention, the formulation of the present invention includes ciprofloxacin, a swelling agent, and at least one of either a

viscolyzing agent and a gelling agent. Together these components form a hydrated gel matrix. The formulation further comprises a gas generating component such that a gas (generally CO_2 but in some cases SO_2) is generated in a controlled manner and is entrapped in the hydrated gel matrix. The swelling agent which belongs to the class of compounds known as superdisintegrants, absorbs large amounts of fluid and causes the matrix to swell significantly. The gas generated by the gas generating component also causes matrix expansion. However, in the present invention, swelling of the matrix is controlled by the viscolyzing agent and/or the gelling agent, which acts both as a swelling and a drug release controlling agent.

The characteristics of the hydrated gel matrix can be modified by altering the ratios and amounts of the swelling agent, the viscolyzing agent and/or the gelling agent, and the gas generating component without loss of physical integrity of the hydrated gel system. The composition can thus be designed to obtain the optimal rate of release of the ciprofloxacin. It has also been found that such a composition when administered with food is retained for longer periods in the stomach, and thereby in the gastrointestinal tract without loss of its physical integrity.

The generated gas influences the drug delivery from the tablets or capsules in ways that are currently not well understood. For example, factors that may influence drug delivery include:

a. the presence of entrapped gas within the matrix can affect the diffusion path length of the drug and thus exerts a release-controlling effect;

b. the presence of entrapped gas within the matrix can affect the rate of surface erosion of the hydrated gel matrix and thus exerts both a hydrodynamic and a release controlling effect;

c. the expanding pressure and the presence of the gas affects the internal structure of the hydrated gel and thus exerts both a hydrodynamic and a release controlling effect; and,

d. the presence of entrapped gas and its expanding pressure affects the influx of the acidic gastric fluid through the pores of the matrix and thus exerts a release-controlling effect.

It should be realized that gas generated in a small volume within the matrix can exert a high pressure. If this exceeds the capillary pressure due to the surface tension of the aqueous fluid, then it will cause the aqueous fluid in a pore to be pushed by the gas allowing the gas to expand until the internal gas pressure equals the capillary pressure. This phenomenon thus would affect the rate of hydration of the matrix and have a role in determining the rate of release of the drug. In systems which cross-link, it will also have an influence on the developing gel structurization.

The various components of the novel formulation will now be described in more detail.

DRUG

According to the present invention, the pharmaceutical composition is in the form of tablets or capsules that provide a controlled rate of delivery (*i.e.*, temporal control, specifically) of ciprofloxacin. The present invention is particularly suitable for controlled rate of delivery of a drug such as ciprofloxacin that does not show uniform dissolution and absorption characteristics throughout the length of the gastrointestinal tract.

The novel pharmaceutical composition is most suited for controlled delivery of drugs that are absorbed only from the upper parts of the gastrointestinal tract with a specific absorption window (*i.e.*, spatial control), *i.e.*, ciprofloxacin (which is absorbed only from the region extending from the stomach to the jejunum). The pharmaceutical composition is particularly suitable for ciprofloxacin because the absorption of the drug is dependent on its solubility characteristics. Ciprofloxacin dissolves at lower pH values and therefore the "absorption window" is predominantly in the stomach or upper parts of the small intestine. In the case of drugs such as ciprofloxacin, the tablet is not transported past the "absorption window" prior to releasing all the drug so that maximum bioavailability can be attained.

Ciprofloxacin itself or its pharmaceutically acceptable salt or ester may be used in the present invention. The amount of ciprofloxacin to be used in the composition is that which is typically administered for a given period of time. According to the present invention, the pharmaceutical composition can incorporate a high dose medicament. Accordingly, the amount of ciprofloxacin

to be used in the present invention typically ranges from about 0.5 mg up to about 1200 mg.

GAS GENERATING COMPONENT

The gas generating component comprises a substance known to produce gas upon contact with gastric fluid. Examples of the gas generating component that may be used in the present invention include carbonates, such as calcium carbonate, potassium carbonate or sodium carbonate, and bicarbonates such as sodium hydrogen carbonate.

The gas generating component interacts with an acid source triggered by contact with water or simply with gastric fluid to generate carbon dioxide that gets entrapped within the hydrated gel matrix of the swelling composition. The gas generating component such as carbonates and bicarbonates may be present in amounts from about 5% to about 15%, by weight of the composition.

These salts can be used alone or in combination with an acid source as a couple. The acid source may be one or more of an edible organic acid, a salt of an edible organic acid, or mixtures thereof. Examples of organic acids that may be used as the acid source in the present invention include, for example: citric acid or its salts such as sodium citrate or calcium citrate; malic acid, tartaric acid, succinic acid, fumaric acid, maleic acid, or their salts; ascorbic acid or its salts such as sodium or calcium ascorbate; glycine, sarcosine, alanine, taurine, glutamic acid, and the like. The organic acid salts that may be used as the acid source in the present invention include, for example, a mono-alkali salt of an organic acid having more than one carboxylic acid functional group, a bialkali

metal salt of an organic acid having more than two carboxylic acid functional groups, and the like. The acid source may be present in an amount from about 0.5% to 15% by weight, preferably from about 0.5% to about 10% by weight, and more preferably from about 0.5 % to about 5% by weight, of the total weight of the composition.

SWELLING AGENT

According to the present invention, the pharmaceutical composition comprises a swelling agent which is capable of swelling to greater than its original volume when coming into contact with an aqueous fluid, such a gastrointestinal fluid. The preferred swelling agent is cross-linked polyvinyl-pyrrolidone; other swelling agents include cross-linked carboxymethylcellulose sodium and the like. These compounds belong to the class of compounds known as super-disintegrants. The swelling agent, which normally swells to several times its original volume in water, exhibits a controlled swelling in the presence of the viscolyzing and/or gelling agent. The swelling agent may be present in an amount from about 3% to about 15% by weight of the total weight of the composition. More preferably, the swelling agent may be present in an amount from about 5% to about 15% by weight of the total weight of the composition.

VISCOLYZING AGENT AND GELLING AGENT

According to the present invention, the pharmaceutical composition comprises a viscolyzing agent which, upon contact with gastrointestinal fluid, instantaneously viscolyzes to trap the gas generated by the gas generating

component. Preferably, the viscolyzing agent comprises of a carbohydrate gum, such as xanthan gum. Other examples of carbohydrate gums include tragacanth gum, gum karaya, guar gum, acacia, and the like. Cellulose ethers of moderate to high viscosity, like hydroxypropyl methylcellulose, can also be used. In the present invention, it has been found that xanthan gum helps in maintaining tablet integrity when stirred in an aqueous medium, and in sustaining the release of the drug.

According to the present invention, the pharmaceutical composition comprises either said viscolyzing agent or a gelling agent or both. The gelling agent is preferably sodium alginate. The gelling agent cross-links with time to form a stable structure which entraps the generated gas. Thus, with the passage of time, the gelling agent results in a hydrodynamically balanced system whereby the matrix is retained in the stomach for an extended period of time. Simultaneously, the viscolyzing agent and the gelling agent provide a tortuous diffusion pathway for the drug, thereby resulting in controlled drug release.

Preferably, the viscolyzing agent and/or the gelling agent are present in an amount from about 0.1% to about 8% by weight of the total weight of the composition. More preferably, the viscolyzing agent and/or the gelling agent are present in an amount from about 0.2% to about 5% by weight of the total weight of the composition.

The successful use of even low amounts of a viscolyzing agent and/or gelling agent such as xanthan gum in providing tablet integrity is indeed

surprising in view of the fact that the pharmaceutical composition of the present invention comprises a gas generating component and a swelling agent which is most frequently employed as a disintegrant. Those skilled in the art can well recognize that both components can result in rapid disintegration of tablets. Tablets containing hydroxypropylcellulose in amounts approximately the same as the amounts of carbohydrate gum in the present invention disintegrate in 10 to 15 minutes when stirred in an acidic medium. Such disintegration can result in a dose dumping effect, *i.e.*, rapid delivery of a large quantity of drug from the system, and is undesirable particularly because controlled drug delivery systems contain several times the amount of drug in a conventional formulation. Granules formed as a result of the disintegration are also emptied from the stomach in a shorter time than intact tablets. The present invention avoids such disintegration with the use of small quantities of a viscolyzing agent, such as a heteropolysaccharide gum, so that tablets or capsules containing a high dose medicament are of an acceptable size to be taken orally.

In preferred embodiments of the present invention, the viscolyzing agent is xanthan gum. Xanthan gum, also known as corn sugar gum, is a high molecular weight (ca. 2×10^6) biosynthetic polysaccharide gum produced by a pure-culture aerobic fermentation of a carbohydrate with Xanthomonas campestris. It is extraordinarily enzymatically resistant.

In preferred embodiments of the present invention, the xanthan gum has a particle size such that at least 50% by weight passes through a sieve with 44 μm mesh aperture (Sieve No. 325, ASTM). In more preferred embodiments, the

xanthan gum has a particle size such that all of it passes through a 44 μm mesh aperture (Sieve No. 325, ASTM).

Preferably, the viscolyzing agent is present in an amount from about 0.1% to about 8%, by weight of the total weight of the composition. More preferably, the viscolyzing agent is present in an amount from about 0.2% to about 5%, by weight of the total weight of the composition.

OTHER EXCIPIENTS

The pharmaceutical composition may also contain other conventional pharmaceutical excipients, for example, water soluble diluents such as lactose, dextrose, mannitol, sorbitol, and the like; water insoluble diluents such as starch, microcrystalline cellulose, powdered cellulose, and the like; or lubricants such as talc, stearic acid or its salt, magnesium stearate, and the like.

PROCESS FOR PREPARATION

According to the present invention, the pharmaceutical composition is prepared by mixing the drug with the gas generating component, the swelling agent, and one or both of the viscolyzing agent and the gelling agent, plus other excipients and lubricants. The blend is directly compressed into tablets or may be filled into capsules. Alternatively, the pharmaceutical composition is prepared by mixing the foregoing ingredients with only one-half of the lubricants. The mixture is roll compacted and then sieved to obtain granules. The granules are then mixed with the remaining lubricants, and filled into capsules or compressed into tablets.

The following table sets forth the various particle size ranges for the ciprofloxacin base (determined using a Malvern Master Sizer) used in the examples described below:

PARTICLE SIZE DISTRIBUTION - CIPROFLOXACIN BASE

Batch No.	1*	2	3	4	5	6	7	8	9	10	11
90% less than 25 µm	22.38 µm	9.01 µm	9.61 µm	9.25 µm	5.0 µm	4.52 µm	5.0 µm	5.0 µm	10.31 µm	19.31 µm	11.98 µm
50% less than 10 µm	3.13 µm	2.24 µm	2.34 µm	2.31 µm	2.0 µm	1.63 µm	2.0 µm	2.0 µm	3.83 µm	4.91 µm	4.59 µm

* This material was supplied as coarse. It was milled to obtain the desired size range.

COATING

According to the present invention, when the pharmaceutical composition is in the form of tablets, it may be coated with a thin layer of a rapidly dissolving water soluble pharmaceutical excipient. A coating of a water soluble excipient results in faster hydration and gas formation than a coating of water soluble polymer and is the preferred coating.

Examples of water soluble pharmaceutical excipients include film formers like cellulose ether polymers, or soluble pharmaceutical diluents like lactose, sucrose, dextrose, mannitol, xylitol, and the like. In a preferred embodiment of the present invention, the water soluble excipient used as a coating is lactose.

The tablets may be coated to a weight build-up of about 1% to about 4%, preferably, about 1% to about 2%. The coating also helps in masking any bitter taste associated with the drug.

The present invention is illustrated by, but is by no means limited to, the following examples:

EXAMPLE 1

This example illustrates the present invention when the active ingredient is ciprofloxacin hydrochloride. Ciprofloxacin is an example of a drug which is absorbed only from the upper part of the intestine. The pharmaceutical composition is given in Table 1.

TABLE 1

Ingredient	Weight (mg/tablet)	% w/w
Ciprofloxacin hydrochloride monohydrate	598.47	55.16
Xanthan Gum (Keltrol TF)	20.00	1.84
Sodium alginate (Keltone LVCR)	15.00	1.38
Cross-linked carboxymethylcellulose (Ac-Di-Sol)	110.00	10.14
Sodium bicarbonate	230.00	21.20
Microcrystalline cellulose (Avicel PH 101)	16.53	1.52
Sodium Chloride	25.0	2.30
Citric Acid	20.0	1.84
Cross-linked polyacrylic acid (Carbopol 971P)	10.0	0.93
Talc	10.00	0.93
Magnesium Stearate	20.00	1.84
Aerosil	10.00	0.93
Total	1085.00	100%

Ciprofloxacin, xanthan gum, sodium alginate, cross-linked carboxymethyl-cellulose, sodium bicarbonate, microcrystalline cellulose, sodium chloride, citric acid, and half of the lubricants were mixed together and sieved through a sieve (British Standard Sieve (BSS) No. 44). The blend was compacted on a roll-compactor and the compact sieved through a sieve (BSS No. 22) to obtain granules. The granules were mixed with the remaining lubricants and Carbopol and then compressed into tablets. The tablets were spray coated with an aqueous coating composition containing 15.8% w/w lactose, 3.18% w/w talc, and 1.587% w/w titanium dioxide to a weight build up of 1% to 1.5%.

The tablets were tested for dissolution in 0.1 N HCl using USP Apparatus 1 with basket speed at 100 rpm. The dissolution results are given in Table 2.

TABLE 2

Time (hrs)	Cumulative Percent Release
1	21.16
2	33.22
4	58.72
6	74.6
8	85.83
10	93.58

EXAMPLE 2

This example illustrates the present invention when the active ingredient is ciprofloxacin base. The pharmaceutical composition is given in Table 3.

TABLE 3

Ingredient	**Weight (mg/tablet)**	**% w/w of tablet**	**% w/w of drug**
Ciprofloxacin base	1000.00	71.43	100.0
Xanthan Gum (Keltrol TF)	15.00	1.07	1.5
Sodium alginate (Keltone LVCR)	10.00	0.71	1.0
Cross-linked polyvinylpyrrolidone (Kollidon CL-M)	150.00	10.71	15.0
Sodium bicarbonate	200.00	14.28	20.0
Magnesium Stearate	15.00	1.07	1.5
Talc	10.00	0.71	10.0
Total	1400.00	100	--

Ciprofloxacin was sifted through British Standard Sieve (BSS) No. 22. Xanthan gum, sodium alginate, sodium bicarbonate, crospovidone and half the quantities of lubricants, namely, magnesium stearate and talc, were sifted through a sieve (BSS No. 44). All the above mentioned sifted ingredients were blended uniformly, compacted on a roll-compactor and the compacts sifted

through a sieve (BSS No. 18) to obtain granules. Remaining magnesium stearate and talc were sifted through a sieve (BSS No. 60) and blended with above granules and limited proportion of granule fines (finer than BSS No. 60) and then compressed into tablets. The tablets were optionally spray coated with an aqueous coating composition containing 15.8% w/w lactose, 3.18% w/w talc and 1.587% w/w titanium dioxide to a weight build up of 1% to 1.5%.

The dissolution results are given in Table 4.

TABLE 4

Time (hrs)	Cumulative Percent Release
1	24.9
2	37.8
4	60.5
6	80.6
8	85.4
10	98.8

EXAMPLE 3

This example illustrates the present invention when the active ingredient is ciprofloxacin hydrochloride. The pharmaceutical composition is given in Table 5.

TABLE 5

Ingredient	Weight (mg/tablet)	% w/w
Ciprofloxacin hydrochloride monohydrate	600.00	61.54
Xanthan Gum (Keltrol TF)	10.00	1.02
Sodium alginate (Keltone LVCR)	25.00	2.57
Cross-linked carboxymethylcellulose (Ac-Di-Sol)	60.00	6.16
Sodium bicarbonate	250.00	25.64
Microcrystalline cellulose (Avicel PH 101)	15.00	1.54
Talc	5.00	0.52
Magnesium Stearate	10.00	1.02
Total	975.00	100%

The tablets were prepared as described in Example 1 except that Ac-Di-Sol was incorporated extragranularly. Tablets were tested for dissolution as described in Example 1. The dissolution results are given in Table 6.

TABLE 6

Time (hrs)	Cumulative Percent Release
1	28.16
2	38.32
4	52.37
6	64.03
8	74.23
10	82.80

EXAMPLE 4

Gastric Retention and Bioavailability Studies

This example demonstrates that tablets prepared according to the present invention are retained for extended periods in the stomach.

The bioadhesive tablet was prepared as a bilayer tablet. The drug layer composition is given in Table 7, and the bioadhesive layer composition is given in Table 8.

TABLE 7

Ingredient	Weight (mg/tablet)
Ciprofloxacin hydrochloride monohydrate	599.99
Hydroxypropylcellulose-L	20.00
Disodium hydrogen phosphate	25.00
Citric Acid	25.00
Talc	7.00
Magnesium Stearate	15.00
Aerosil 200	10.00
Total	701.99

TABLE 8

Ingredient	Weight (mg/tablet)
Hydroxypropyl methylcellulose (Methocel K4M)	215.00
Cross-linked polyacrylic acid (Carbopol 934 P)	75.00
Dicalcium phosphate	145.00
Sodium benzoate	8.00
Talc	2.00
Aerosil-200	2.50
Sunset Yellow	2.50
Total	450.00

The tablets were prepared by conventional steps of mixing, roll compaction, sieving, blending with the lubricants and compression into bi-layered tablets. 70 mg of barium sulphate was incorporated into the bioadhesive layer to function as x-ray contrast medium. Gastric retention studies of the bioadhesive bi-layered tablets were done on healthy male volunteers who were

given two tablets following a standard breakfast. X-ray images were recorded periodically. The bioadhesive tablets were retained in the stomach for 2.5 to 3.5 hrs.

Hydrophilic matrix tablets with the composition given in Table 9 were also prepared.

TABLE 9

Ingredient	Weight (mg/tablet)
Ciprofloxacin hydrochloride monohydrate	599.99
Hydroxypropyl methylcellulose (Methocel K4M)	20.00
Hydroxypropylcellulose-L	40.00
Citric Acid	25.00
Disodium hydrogen phosphate	25.00
Talc	10.00
Magnesium Stearate	10.00
Total	729.99

70mg of barium sulfate was also incorporated into the above composition. The tablets were prepared by conventional steps of mixing, roll compaction, sieving, blending with the lubricants and compression into tablets.

Floating capsules with the composition given in Table 10 were also prepared.

TABLE 10

Ingredient	Weight (mg/capsule)
Ciprofloxacin hydrochloride monohydrate	599.99
Hydroxypropyl methylcellulose (Methocel K4M)	30.00
Hydroxypropylcellulose-L	30.00
Citric Acid	5.00
Disodium hydrogen phosphate	5.00
Talc	4.00
Magnesium Stearate	6.00
Total	679.99

50 mg of barium sulphate was incorporated into the above composition. Gastric retention studies were done on healthy male volunteers who were given two tablets/capsules after a standard breakfast. X-ray images were recorded periodically. The hydrophilic matrix tablets were retained for 2 to 2.5 hrs, and the floating capsules for 3.5 to 4.5 hrs.

Gastric retention studies were also done on the ciprofloxacin base formulation of a similar composition as given in Example 2. The volunteers were given two tablets after a standard breakfast. Magnetic resonance imaging confirmed that the tablets according to the present invention were retained in the stomach for a period of 5 to 7 hrs.

In another experiment, a randomized, three-treatment, three period, cross-over pilot bioavailability study was conducted for formulation A (two ciprofloxacin hydrochloride 500 mg tablets, for once-daily administration, prepared according to Example 1), formulation B (ciprofloxacin free base 1000

mg tablets, for once-daily administration, prepared according to Example 2), and reference formulation R (Cipro™ (Bayer Corp.) 500 mg immediate release tablets given twice daily). The tablets were administered 30 minutes after a standard breakfast. The mean serum concentration-time profile is given in Figure 1. Figure 1 is based on the following data listed in Table 11, below.

TABLE 11

Time (Hr)	Mean Concentrations (mcg/mL)		
	A	B	R
0	0.0000	0.0000	0.0000
0.5	*	*	0.30000
1	0.0489	0.3720	1.8379
1.5	*	*	2.0779
2	0.1557	0.9940	1.8546
2.5	*	*	1.6348
3	1.1806	1.5004	1.3731
4	2.7070	2.1164	1.0868
5	2.8478	1.8898	0.7638
6	1.7944	1.3594	0.5404
8	1.2467	0.9494	0.3579
10	0.9367	0.7855	0.2323
12	0.6503	0.8714	0.1687
12.5	*	*	0.1594
13	*	*	0.3916
13.5	*	*	0.8982
14	0.4171	0.6831	1.0993
14.5	*	*	1.1432
15	*	*	1.3889
16	0.2753	0.4826	1.1187
17	*	*	0.9377
18	0.1901	0.3812	0.7633
20	*	*	0.4864
22	*	*	0.3766
24	0.1039	0.1778	0.2825

A: 500 mg X 2 OD Fed (FDA Meal)
B: 1000 mg OD, Fed (FDA Meal)
R: 500 mg b.l.d. Fed (FDA Meal)
*For OD formulation these sampling points were not included

Both the once-daily formulations (A and B) gave an extent of absorption comparable to the immediate release tablets (R). Thus, it can be inferred that

the time period of release of drug into gastric fluid was adjusted such that it was about the same as or less than the retention time of the tablets at the site of absorption. Furthermore, formulation B gave a serum concentration time profile that would be desirable for a once-daily formulation in that the peak serum concentration was comparable to that for the immediate release drug, and the effective serum concentrations of the drug were maintained for longer periods.

EXAMPLE 5

In some respects, formulation B of the prior Example did not give as good results as the twice-daily Cipro™ 500 mg tablets. For example, the Area Under the Curve above the Minimum Inhibitory Concentration (AUC above MIC) for formulation B was less than that of conventional Cipro™ tablets.

An improved once-daily 1,000 mg ciprofloxacin free base formulation (the "OD" formulation) was developed, the composition of which is given in Table 12. In the OD formulation, the amount of gelling agent (sodium alginate) is about one-half that of formulation B (0.49% vs. 1.0%).

TABLE 12

Ingredients	Weight (mg/tablet)	% w/w of the drug
Ciprofloxacin base	1000.0	69.9
Sodium alginate	5.0	0.34
Xanthan gum	15.0	1.03
Sodium bicarbonate	200.0	13.74
Cross-Linked polyvinyl pyrrolidone (Kollidon CL-M)	176.8	12.15
Magnesium stearate	33.0	2.26
Talc	10.0	0.68
Total	1440	100

Tablets were prepared from the components in Table 12 and tested for dissolution as described earlier. Remarkably, it was observed that the *in vitro* dissolution profile of the OD formulation (Table 13) was much faster releasing than formulation B. Thus, more than 80% of the drug in the OD tablets was released within 4 hours as compared to 8 hours for formulation B. Compare Table 12 with Table 13.

TABLE 13

Time (hrs.)	Cumulative percent Release
1	35.49
2	53.61
4	82.33
6	98.72

The mean stomach retention of the OD tablets was studied by magnetic resonance imaging and was found to be 5.33 hours which correlated well with the 6 hour dissolution profile of these tablets.

In order to compare the pharmacokinetic and pharmacodynamic parameters of this once daily formulation, a randomized, three period, balanced crossover bioavailability study was conducted in 12 healthy, adult male human subjects, between 18-45 years of age where one dose of ciprofloxacin 1000 mg OD tablets was administered 30 minutes after a standard high fat breakfast. The immediate release Cipro™ tablets were tested under both fed and fasted conditions.

Under fed conditions, two oral doses of 500 mg immediate release Cipro™ tablets were given. The first oral dose was given within 30 minutes of a high fat breakfast and the second dose was given 12 hours later after a high fat meal (dinner).

Under fasted conditions, two oral doses of 500 mg tablets of the Cipro™ immediate release tablets were administered. The first oral dose was given after an overnight fast, and the second oral dose was given 12 hours later but four hours after a light meal.

The results of the study are shown in Figs. 2 and 3, where Fig. 2 shows the plasma concentration over time of the OD tablets (fed) vs. Cipro™ (fed), and Fig. 3 shows the plasma concentration of the OD tablets (fed) vs. Cipro™ (fasted). Figures 2 and 3 are based on the following data listed in Table 14 and Table 15, respectively, below.

TABLE 14

Time (Hr)	Mean Concentrations (mcg/mL)	
	A	C
0	0.0000	0.0000
0.5	0.2190	*
1	1.0964	0.3430
1.5	1.9702	*
2	2.0397	0.9751
2.5	1.8232	*
3	1.5617	1.6335
4	1.2265	2.6216
5	1.0123	2.9162
6	0.7777	2.0336
8	0.5291	1.4256
10	0.3527	1.3841
12	0.2608	0.9790
12.5	0.3159	*
13	0.4176	*
13.5	0.8401	*
14	1.9238	0.5942
14.5	1.8384	*
15	1.6543	*
16	1.2336	0.4393
17	0.9689	*
18	0.8258	0.3357
20	0.5962	*
22	0.4366	*
24	0.3653	0.1843

A: 500 mg b.I.d. Fed (FDA Meal)
C: 1000 mg OD Fed (FDA Meal)
*For OD formulation these sampling points were not included

TABLE 15

Time (Hr)	Mean Concentrations (mcg/mL)	
	B	C
0	0.0000	0.0000
0.5	1.3580	*
1	2.4747	0.3430
1.5	2.7413	*
2	2.3684	0.9751
2.5	2.0204	*
3	1.5997	1.6335
4	1.1985	2.6216
5	0.9429	2.9162
6	0.7298	2.0336
8	0.5172	1.4256
10	0.3575	1.3841
12	0.2709	0.9790
12.5	0.9855	*
13	2.5113	*
13.5	2.7718	*
14	2.4376	0.5942
14.5	1.9856	*
15	1.7173	*
16	1.1702	0.4393
17	0.8631	*
18	0.7360	0.3357
20	0.5095	*
22	0.4207	*
24	0.3431	0.1843

B: 500 mg b.l.d. Fasting
C: 1000 mg OD Fed (FDA Meal)
*For OD formulation these sampling points were not included

The OD formulation gave a plasma concentration time profile desirable for once daily dosage form in that the peak plasma concentration (Cmax) was comparable to that for the immediate release drug indicating a similar rate of absorption of the drug. The total bioavailability of the drug $AUC_{(0-\infty)}$ (Area Under the Curve) was also comparable to that of immediate release tablets indicating that all of the drug is released from the formulation during its residence time in the stomach. See Table 16.

TABLE 16

Study	Cmax (µg/ml)	AUC $_{(0-\infty)}$ (µg.h/ml)
Ciprofloxacin 1000 mg. OD (Fed)	3.04	24.81
Cipro™ 500 mg Bid (Fasted)	3.17	26.28
Cipro™ 500 Mg Bid (Fed)	2.66	22.39

Table 17 gives the AUC above MIC at the three levels of 0.1µg/ml, 0.25 µg/ml and 0.5 µg/ml for ciprofloxacin OD 1000 mg vs. Cipro™ 500 mg bid. These values for ciprofloxacin OD were better than those for Cipro™ immediate release tablets administered twice daily under fed conditions, indicating better therapeutic efficacy of the OD formulation when both immediate and controlled dosage forms were administered after food. The therapeutic efficacy of the OD tablets under fed condition was comparable to the therapeutic efficacy of the Cipro™ immediate release tablets administered under fasting conditions.

Based on the above results seen in Figures 1, 2, and 3, it is anticipated that a sustained release solid dosage form of ciprofloxacin would have to provide pharmacokinetic performance as measured by mean serum concentration, area under the serum/plasma concentration–time curve above minimum inhibitory concentrations and durations above minimum inhibitory serum/plasma concentrations of at least 70% as compared to immediate release divided dose treatment. While the above results have been specifically identified for 1,000 mg tablets, it is anticipated that 100-1,000 mg tablets of ciprofloxacin, orally administered to humans under fed conditions, would provide a medicament

serum/plasma concentration – time curve with an area under the curve (time zero to infinity), ranging from 3.5 to about 30 μg-hours/ml. Similarly, it is anticipated that the 100 mg-1,000 mg tablets would provide a mean peak serum/plasma concentration ranging from about 0.5 to about 4 μg/ml. Further, it is anticipated that the 100 mg-1,000 mg tablets would provide a medicament serum/plasma concentration - time curve with an area under the curve (above a minimum inhibitory concentration of 0.1 μg/ml), ranging from about 3 to about 26 μg-hours/ml. It is also anticipated that the 100 mg-1,000 mg tablets would provide a medicament serum/plasma concentration – time curve with an area under the curve (above a minimum inhibitory concentration of 0.25 μg/ml), ranging from about 2 to about 22 μg-hours/ml. Finally, it is anticipated that they 100 mg-1,000 mg tablets would provide a medicament serum/plasma concentration - time curve with an area under the curve (above a minimum inhibitory concentration of 0.5 μm/ml), ranging from about 1 to about 18 μg-hours/ml.

TABLE 17
AUC above MIC

Treatment	0.1 μg/ml.h	0.25 μg/ml.h	0.5 μg/ml.h
Ciprofloxacin base 1000 mg, OD (Fed)	20.7 ± 4.4	17.4 ± 4.3	13.2 ± 4.1
Cipro™ 2 x 500 mg bid (Fasted)	21.5 ± 3.7	18.0 ± 3.8	13.4 ± 4.0
Cipro™ 2 x 500 mg bid (Fed)	17.68 ± 3.9	14.2 ± 3.9	9.7 ± 3.4

Thus, a minor change in the percentage of hydrophilic polymer (sodium alginate) from 0.71% w/w of the composition to 0.34% w/w of the composition resulted in a dramatic and unexpected improvement in the pharmacodynamic

and pharmacokinetic parameters, which are important measures of therapeutic efficacy.

EXAMPLE 6

This example illustrates the present invention when the active ingredient is ciprofloxacin base:

TABLE 18

Ingredient	**Weight (mg/tablet)**	**% w/w**
Ciprofloxacin	1012.10	68.53
Xanthan Gum	45.0	3.05
Sodium Bicarbonate	200	13.54
Crospovidone	176.82	11.97
Magnesium Stearate	33	2.23
Talc	10	0.68
Total	1476.92	100

The tablets were prepared as described in Example 2. The tablets were tested for dissolution as described in Example 1. The dissolution results are given in Table 19.

TABLE 19

Time (hrs)	Cumulative Percent Release
1	34
2	51.4
4	69.0
6	94.8
8	100.5

EXAMPLE 7

This example illustrates the present invention when the active ingredient is ciprofloxacin base:

TABLE 20

Ingredient	**Weight (mg/tablet)**	**% w/w**
Ciprofloxacin	1012.10	69.47
Sodium Alginate	25	1.72
Sodium Bicarbonate	200	13.73
Crospovidone	176.82	12.14
Magnesium Stearate	33	2.27
Talc	10	0.69
Total	1456.92	100.02

The tablets were prepared as described in Example 2. The tablets were tested for dissolution as described in Example 1. The dissolution results are given in Table 21.

TABLE 21

Time (hrs.)	Cumulative Percent Release
1	34.6
2	52
3	68.4
4	79.5
6	92.4
8	95.7

EXAMPLE 8

This example illustrates the present invention when the active ingredient is ciprofloxacin base:

TABLE 22

Ingredient	**Weight (mg/tablet)**	**% w/w**
Ciprofloxacin	1012.10	69
Sodium Alginate	5.0	0.34
Sodium Bicarbonate	200	13.63
Crospovidone	176.82	12.05
Magnesium Stearate	33	2.25
Talc	10	0.68
Methocel K15M	30	2.04
Total	1466.92	99.99

The tablets were prepared as described in Example 2. The tablets were tested for dissolution as described in Example 1. The dissolution results are given in Table 23.

TABLE 23

Time (hrs.)	Cumulative Percent Release
1	43.6
2	57.6
3	74.4
4	87.0
6	97.5
8	100.2

EXAMPLE 9

This example illustrates the present invention when the active ingredient is ciprofloxacin base:

TABLE 24

Ingredient	**Weight (mg/tablet)**	**% w/w**
Ciprofloxacin	1015.18	75.15
Sodium Alginate	5.0	0.37
Xanthan Gum	15	1.11
Sodium Bicarbonate	200	14.8
Crospovidone	72.75	5.39
Magnesium Stearate	33	2.44
Talc	10	0.74
Total	1350.93	100

The tablets were prepared as described in Example 2. The tablets were tested for dissolution as described in Example 1. The dissolution results are given in Table 25.

TABLE 25

Time (hrs.)	Cumulative Percent Release
1	39.2
2	54.2
3	72.39
4	84.9
6	100.29

EXAMPLE 10

This example illustrates the present invention when the active ingredient is ciprofloxacin base:

TABLE 26

Ingredient	Weight (mg/tablet)	% w/w
Ciprofloxacin	1015.18	67.35
Sodium Alginate	5.0	0.33
Xanthan Gum	15	1.0
Crospovidone	176.82	11.73
Magnesium Stearate	33	2.19
Talc	10	0.66
Sodium Carbonate	252.32	16.74
Total	1507.32	100

The tablets were prepared as described in Example 2. The tablets were tested for dissolution as described in Example 1. The dissolution results are given in Table 27.

TABLE 27

Time (hrs.)	Cumulative Percent Release
1	31.34
2	59.86
3	75.3
4	81.69
6	90.39
8	91.5

EXAMPLE 11

This example illustrates the present invention when the active ingredient is ciprofloxacin base:

TABLE 28

Ingredient	Weight (mg/tablet)	% w/w
Ciprofloxacin	1015.18	69.66
Sodium Alginate	7.28	0.5
Xanthan Gum	15	1.03
Sodium Bicarbonate	200	13.72
Crospovidone	176.82	12.13
Magnesium Stearate	33	2.26
Talc	10	0.69
Total	1457.28	99.99

The tablets were prepared as described in Example 2. The tablets were tested for dissolution as described in Example 1. The dissolution results are given in Table 29.

TABLE 29

Time (hrs.)	Cumulative Percent Release
1	40.06
2	59.26
3	86.19
4	96.39
6	100.2

EXAMPLE 12

This example illustrates the present invention when the active ingredient is ciprofloxacin base:

TABLE 30

Ingredient	Weight (mg/tablet)	% w/w
Ciprofloxacin	1015.18	70.43
Sodium Alginate	5.0	0.35
Xanthan Gum	1.46	0.1
Sodium Bicarbonate	200	13.87
Crospovidone	176.82	12.27
Magnesium Stearate	33	2.29
Talc	10	0.69
Total	1441.46	100

The tablets were prepared as described in Example 2. The tablets were tested for dissolution as described in Example 1. The dissolution results are given in Table 31.

TABLE 31

Time (hrs.)	Cumulative Percent Release
1	33.34
2	58.94
3	76.11
4	83.91
6	95.7

EXAMPLE 13

This example illustrates the present invention when the active ingredient is ciprofloxacin base:

TABLE 32

Ingredient	Weight (mg/tablet)	% w/w
Ciprofloxacin	1015.18	69.44
Sodium Alginate	5.0	0.34
Xanthan Gum	21.83	1.5
Sodium Bicarbonate	200	13.68
Crospovidone	176.82	12.1
Magnesium Stearate	33	2.26
Talc	10	0.68
Total	1461.83	100

The tablets were prepared as described in Example 2. The tablets were tested for dissolution as described in Example 1. The dissolution results are given in Table 33.

TABLE 33

Time (hrs.)	Cumulative Percent Release
1	44.2
2	61.86
3	87.9
4	98.7
6	106.95

EXAMPLE 14

This example illustrates the present invention when the active ingredient is ciprofloxacin base:

TABLE 34

Ingredient	Weight (mg/tablet)	% w/w
Ciprofloxacin	1016.19	72.51
Sodium Alginate	5.0	0.36
Xanthan Gum	15	1.07
Sodium Bicarbonate	145.5	10.38
Crospovidone	176.82	12.61
Magnesium Stearate	33	2.35
Talc	10	0.71
Total	1401.51	99.99

The tablets were prepared as described in Example 2. The tablets were tested for dissolution as described in Example 1. The dissolution results are given in Table 35.

TABLE 35

Time (hrs.)	Cumulative Percent Release
1	44.46
2	56.8
3	65.91
4	74.19
6	89.31
8	98.49

Table 36 below summarizes Examples 5-14 above with respect to their ingredients and includes the dissolution profile of each formulation.

TABLE 36

Ingredient	% w/w in Example									
	5	6	7	8	9	10	11	12	13	14
Ciprofloxacin base	69.9	68.53	69.47	69.	75.15	67.35	69.66	70.43	69.44	72.15
Xanthan gum 0.5-2.0	1.03	3.05	None	None	1.11	1.0	1.03	0.1	1.5	1.07
Sodium alginate 0.2-0.9	0.34	None	1.72	0.34	0.37	0.33	0.5	0.35	0.34	0.36
XL polyvinylpyrrolidone 5-20	12.15	11.97	12.14	12.05	5.39	11.73	12.13	12.27	12.1	12.61
Sodium bicarbonate 10-25	13.74	13.54	13.73	13.63	14.8	None	13.72	13.87	13.68	10.38
Sodium carbonate						16.74				
Methocel K 15 M				2.04						
[Ratio Xanthan:Alginate] 10:1-1:1	3.03:1	NA	NA	NA	3:1	3.03:1	2.06:1	0.29:1	4.41:1	2.97:1
Time (hours)	**Percent Cumulative Release**									
1	35.49	34.	34.6	43.6	39.2	31.4	40.06	33.34	44.2	44.46
2	53.61	51.4	52.	57.6	54.2	59.86	59.26	58.94	61.86	56.8
3			68.4	74.4	72.4	75.3	86.19	76.11	87.9	65.91
4	82.33	69.	79.5	87.0	84.9	81.69	96.39	83.91	98.7	74.19
6	98.72	94.8	92.4	97.5	100.29	90.39	100.2	95.7	106.95	89.31
8		100.5	95.7	100.2		91.5				98.49

EXAMPLE 15

This example illustrates the present invention when the active ingredient is ciprofloxacin base:

TABLE 37

Ingredient	**Weight (mg/tablet)**	**% w/w**
Ciprofloxacin	1015.18	67.98
Sodium Alginate	5.0	0.003
Xanthan Gum	15.0	0.01
Crospovidone	176.82	11.84
Mag. Stearate	33.0	2.21
Talc	10.0	0.67
Calcium Carbonate	238.27	15.96
Total	1493.27	98.673

The tablets were prepared as described in Example 2. The tablets were tested for dissolution as described in Example 1. The dissolution results are given in Table 38.

TABLE 38

Time (hrs.)	Cumulative Percent Release
1	44.4
2	62.4
3	73.11
4	78.0
6	84.09
8	87.0

EXAMPLE 16

This example illustrates the present invention when the active ingredient is ciprofloxacin base:

TABLE 39

Ingredient	Weight (mg/tablet)	% w/w
Ciprofloxacin	1015.18	69.32
Sodium Alginate	14.55	0.009
Xanthan Gum	15.0	0.01
Sod. Bicarbonate	200.0	13.66
Crospovidone	176.82	12.07
Magnesium Stearate	33.0	2.25
Talc	10.0	0.68
TOTAL	1464.55	97.32

The tablets were prepared as described in Example 2. The tablets were tested for dissolution as described in Example 1. The dissolution results are given in Table 40.

TABLE 40

Time (hrs.)	Cumulative Percent Release
1	37.9
2	45.06
3	65.91
4	71.1
6	78.81

EXAMPLE 17

This example illustrates the present invention when the active ingredient is ciprofloxacin base:

TABLE 41

Ingredient	Weight (mg/tablet)	% w/w
Ciprofloxacin	1015.18	67.11
Sodium Alginate	5.0	0.003
Xanthan Gum	72.75	4.81
Sodium Bicarbonate	200.0	13.22
Crospovidone	176.82	11.69
Magnesium Stearate	33.0	2.18
Talc	10.0	0.006
TOTAL	1512.75	99.019

The tablets were prepared as described in Example 2. The tablets were tested for dissolution as described in Example 1. The dissolution results are given in Table 42.

TABLE 42

Time (hrs.)	Cumulative Percent Release
1	32.26
2	47.2
3	63.3
4	74.01
6	94.2

Other than the above experiments, the following formulations were made into tablets as described above. Dissolution and floating characteristics testing

was also done for the following formulations. One or the other, *i.e.*, the dissolution profile or floating characteristics, were found to be unsatisfactory in comparison to the above examples, for tablets according to the following formulations:

TABLE 43

Ingredient	**Example 18**	**Example 19**
Ciprofloxacin	1015.18	1015.18
Sodium Alginate	0	5.0
Xanthan Gum	15.0	0
Sodium Bicarbonate	200.0	200.0
Crospovidone	176.82	176.82
Magnesium Stearate	33.0	33.0
Talc	10.0	10.0
TOTAL	1450.00	1440.0
DISSOLUTION		
Time (hrs.)	Cumulative Percent Release	
1	68.8	52.5
2	93.2	68.94
3	104.1	90.39
4	-	100.8
6	-	104.79
8	-	-

TABLE 44

Ingredients	Example 20	Example 21	Example 22	Example 23	Example 24
Ciprofloxacin	1016.19	1016.19	1012.1	1016.19	1012.1
Sodium Alginate	5.0	5.0	5.0	5.0	5.0
Sodium Bicarbonate	200.0	200.0	200.0	200.0	200.0
Crospovidone	176.82	176.82	176.82	176.82	176.82
Magnesium Stearate	33.0	33.0	33.0	33.0	33.0
Talc	10.0	10.0	10.0	10.0	10.0
Methocel K15M	15.0	-	-	-	-
Gellan Gum (Gelrite)	-	15.0	30.0	-	-
Carrageenan	-	-	-	15.0	45.0
TOTAL	1456.01	1456.01	1466.92	1456.01	1481.92
DISSOLUTION					
Time (hrs.)	Cumulative Percent Release				
1	48.66	50.74	49.6	72.46	88.8
2	63.54	62.86	58.2	81.54	93.2
3	80.31	74.19	67.2	87.09	97.8
4	89.49	80.79	74.4	92.1	99.0
6	100.11	91.71	88.2	96.45	100.2
8	101.7	99.99	95.1	97.11	101.1

TABLE 45

Ingredients	Example 25	Example 26	Example 27	Example 28	Example 29	Example 30
Ciprofloxacin	1015.18	1012.1	1015.18	1012.1	1015.18	1012.1
Xanthan Gum	15.0	15.0	15.0	15.0	15.0	15.0
Sodium Bicarbonate	200.0	200.0	200.0	200.0	200.0	200.0
Crospovidone	176.82	176.82	176.82	176.82	176.82	176.82
Magnesium Stearate	33.0	33.0	33.0	33.0	33.0	33.0
Talc	10.0	10.0	10.0	10.0	10.0	10.0
Carbopol 971 P	5.0	10.0	-	-	-	-
Methyl Cellulose	-	-	5.0	20.0	-	-
Eudragit EPO	-	-	-	-	5.0	30.0
TOTAL	1455.0	1446.92	1455.0	1456.92	1455.0	1466.92
DISSOLUTION						
Time (hrs.)	Cumulative Percent Release					
1	45.2	56.8	74.26	68.2	94.26	101.4
2	59.34	67.0	87.06	83.0	94.94	-
3	71.79	76.8	95.61	92.4	97.89	-
4	80.91	84.9	97.71	95.4	98.79	-
6	92.01	95.1	99.21	99.0	-	-
8	93.0	97.5	100.59	100.8	-	-

TABLE 46

Ingredient	Example 31	Example 32	Example 33	Example 34	Example 35	Example 36
Ciprofloxacin	1015.18	1012.1	1015.18	1012.1	1015.18	1012.1
Sodium Alginate	5.0	5.0	5.0	5.0	5.0	5.0
Xanthan Gum	15.0	15.0	15.0	15.0	15.0	15.0
Sodium Bicarbonate	200.0	200.0	200.0	200.0	200.0	200.0
Magnesium Stearate	33.0	33.0	33.0	33.0	33.0	33.0
Talc	10.0	10.0	10.0	10.0	10.0	10.0
Ac-di-sol	176.82	100.0	-	-	-	-
Sodium Starch glycolate	-	-	176.82	125.0	-	-
MCC (Avicel pH 101)	-	-	-	-	176.82	125.0
TOTAL	1455.0	1375.1	1455.0	1400.1	1455.0	1400.1
DISSOLUTION						
Time (hrs.)	Cumulative Percent Release					
1	42.86	47.6	57.46	53.8	67.4	62.6
2	51.4	55.8	65.6	62.4	79.26	74.4
3	60.21	62.4	72.81	70.8	86.7	84.9
4	66.81	67.5	77.19	75.6	91.5	88.2
6	81.09	76.2	84.69	82.4	95.49	94.8
8	87.6	83.1	92.31	88.2	98.79	97.2

TABLE 47

Ingredient	Example 37	Example 38	Example 39
Ciprofloxacin	1015.18	1015.18	1015.18
Sodium Alginate	5.0	5.0	5.0
Xanthan Gum	15.0	15.0	15.0
Sodium Bicarbonate	200.0	200.0	200.0
Crospovidone	0	261.9	363.75
Magnesium Stearate	33.0	33.0	33.0
Talc	10.0	10.0	10.0
TOTAL	1278.18	1540.08	1641.93
DISSOLUTION			
Time (hrs.)	Cumulative Percent Release		
1	66.66	49.2	57.26
2	79.8	75.66	77.74
3	91.2	96.99	106.2
4	94.71	100.71	-
6	97.59	-	-

TABLE 48

Ingredients	**Example 40**	**Example 41**	**Example 42**
Ciprofloxacin	1016.19	1016.19	1016.19
Sodium Alginate	5.0	5.0	5.0
Sodium Bicarbonate	200.0	200.0	200.0
Crospovidone	176.82	176.82	176.82
Magnesium Stearate	33.0	33.0	33.0
Talc	10.0	10.0	10.0
Methocel K15M	15.0	-	-
Gellan gum (Gelrite)	-	15.0	-
Carrageenan	-	-	15.0
TOTAL	1456.01	1456.01	1456.01
DISSOLUTION			
Time (hrs.)	Cumulative Percent Release		
1	48.66	50.74	72.46
2	63.54	62.86	81.54
3	80.31	74.19	87.09
4	89.49	80.79	92.1
6	100.11	91.71	96.45
8	101.7	99.99	97.11

TABLE 49

Ingredients	Example 43	Example 44	Example 45
Ciprofloxacin	1015.18	1015.18	1015.18
Xanthan Gum	15.0	15.0	15.0
Sodium Bicarbonate	200.0	200.0	200.0
Crospovidone	176.82	176.82	176.82
Magnesium Stearate	33.0	33.0	33.0
Talc	10.0	10.0	10.0
Carbopol 971 P	5.0	-	-
Methyl Cellulose	-	5.0	-
Eudragit EPO	-	-	5.0
TOTAL	1455.01	1455.01	1455.01
DISSOLUTION			
Time (hrs.)	Cumulative Percent Release		
1	45.2	74.26	94.26
2	59.34	87.06	94.94
3	71.79	95.61	97.89
4	80.91	97.71	98.79
6	92.01	99.21	-
8	93.0	100.59	-

TABLE 50

Ingredients	Example 46	Example 47	Example 48
Ciprofloxacin	1015.18	1015.18	1015.18
Sodium Alginate	5.0	5.0	5.0
Xanthan Gum	15.0	15.0	15.0
Sodium Bicarbonate	200.0	200.0	200.0
Magnesium Stearate	33.0	33.0	33.0
Talc	10.0	10.0	10.0
Ac-di-sol	176.82	-	-
Sodium Starch glycolate	-	176.82	-
MCC (Avicel pH 101)	-	176.82	-
TOTAL	1455.0	1455.0	1455.0
DISSOLUTION			
Time (hrs.)	Cumulative Percent Release		
1	42.86	57.46	67.4
2	51.4	65.6	79.26
3	60.21	72.81	86.7
4	66.81	77.19	91.5
6	81.09	84.69	95.49
8	87.6	92.31	98.79

TABLE 51

Ingredients	**Example 49**
Ciprofloxacin	1015.18
Sodium Alginate	5.0
Xanthan Gum	15.0
Crospovidone	176.82
Magnesium Stearate	33.0
Talc	10.0
Potassium Bicarbonate	238.34
TOTAL	1493.34
DISSOLUTION	
Time (hrs.)	Cumulative Percent Release
1	69.06
2	77.74
3	85.2
4	87.0
6	87.0
8	98.1

TABLE 52

Ingredient	Example 50	Example 51
Ciprofloxacin	1015.18	1015.18
Sod. Alginate	0	1.46
Xanthan Gum	15.0	15.0
Sodium Bicarbonate	200.0	200.0
Crospovidone	176.82	176.82
Magnesium Stearate	33.0	33.0
Talc	10.0	10.0
TOTAL	1450.00	1451.46
DISSOLUTION		
Time (hrs.)	Cumulative Percent Release	
1	68.8	51.46
2	93.2	65.34
3	104.1	84.39
4	-	92.79
6	-	97.41

TABLE 53

Ingredient	**Example 52**
Ciprofloxacin	1015.18
Sodium Alginate	5.0
Sodium Bicarbonate	200.0
Crospovidone	176.82
Magnesium Stearate	33.0
Talc	10.0
TOTAL	1440.0
DISSOLUTION	
Time (hrs.)	Cumulative Percent Release
1	52.5
2	68.94
3	90.39
4	100.8
6	104.79

TABLE 54

Ingredient	Example 53	Example 54	Example 55	Example 56
Ciprofloxacin	1015.18	1016.19	1015.18	1015.18
Sodium Alginate	5.0	5.0	5.0	5.0
Xanthan Gum	15.0	15.0	15.0	15.0
Sodium Bicarbonate	0	72.75	291.0	436.5
Crospovidone	176.82	176.82	176.82	176.82
Magnesium Stearate	33.0	33.0	33.0	33.0
Talc	10.0	10.0	10.0	10.0
TOTAL	1255.0	1328.76	1546.0	1691.5
DISSOLUTION				
Time (hrs)	% released			
1	73.06	50.86	49.0	42.46
2	73.7	63.6	72.14	74.66
3	-	73.89	96.3	96.6
4	94.8	83.7	103.8	104.1
6	87.9	93.51	-	-
8	-	98.19	-	-

While the invention has been described by reference to specific examples, this was for purposes of illustration only. Numerous alternative embodiments will be apparent to those skilled in the art and are considered to be within the scope of the invention.

CLAIMS

1. A once daily tablet formulation for oral administration in humans for the controlled release of ciprofloxacin comprising a pharmaceutically effective amount of ciprofloxacin, from about 0.1% to about 8.0% of a viscolyzing agent and/or a gelling agent, about 5.0% to about 15% of a gas generating agent, and about 3.0% to about 15% of a swelling agent, said percentages being w/w of the composition.

2. A once daily tablet formulation for oral administration in humans for the controlled release of ciprofloxacin comprising a pharmaceutically effective amount of ciprofloxacin, from about 0.2% to about 5.0% of a viscolyzing agent and/or a gelling agent, about 5.0% to about 15% of a gas generating agent, and about 5.0% to about 15% of a swelling agent, said percentages being w/w of the composition.

3. The formulation of claim 1 or 2, wherein the viscolyzing agent is either a carbohydrate gum or cellulose ethers.

4. The formulation of claim 3, wherein the carbohydrate gum is xanthan gum and the cellulose ether is hydroxypropyl methylcellulose. (methocel).

5. The formulation of claim 1 or 2, wherein the gelling agent is sodium alginate.

6. The formulation of claim 1 or 2, wherein either or both the viscolyzing agent and gelling agent are used.

7. The formulation of claim 6, wherein the viscolyzing agent is xanthan gum.

8. The formulation of claim 3, wherein the gas generating agent is selected from the group consisting of sodium bicarbonate, calcium carbonate, sodium carbonate, and mixtures thereof.

9. The formulation of claim 3, wherein the swelling agent is crosslinked polyvinylpyrrolidone.

10. A once daily formulation for oral administration in humans for the controlled release of ciprofloxacin comprising a pharmaceutically effective amount of ciprofloxacin, about 0.2% to about 0.5% sodium alginate, about 0.5 to about 2.0% xanthan gum, about 10.0% to about 25% sodium bicarbonate, and about 5.0% to about 20% cross-linked polyvinylpyrrolidone, said percentages being w/w of the composition, wherein the weight ratio of sodium alginate to xanthan gum is between about 1:1 to about 1:10.

11. The formulation of claim 10 comprising 69.9% ciprofloxacin base, 0.34% sodium alginate, 1.03% xanthan gum, 13.7% sodium

bicarbonate, 12.1% cross-linked polyvinylpyrrolidone, and optionally other pharmaceutical excipients.

12. The formulation of claim 10 in the form of a tablet.

13. A once daily homogenous, single layer tablet formulation for oral administration in humans for the controlled release of ciprofloxacin in the stomach or upper part of the small intestine comprising a pharmaceutically effective amount of ciprofloxacin, about 0.2% to about 0.5% sodium alginate, about 0.5 to about 2.0% xanthan gum, about 10.0% to about 25% sodium bicarbonate, and about 5.0% to about 20% cross-linked polyvinylpyrrolidone, said percentages being w/w of the composition, wherein the weight ratio of sodium alginate to xanthan gum is between about 1:1 to about 1:10.

14. The formulation of claim 13 comprising 69.9% ciprofloxacin base, 0.34% sodium alginate, 1.03% xanthan gum, 13.7% sodium bicarbonate, 12.1% cross-linked polyvinylpyrrolidone, and optionally other pharmaceutical excipients.

15. A once daily tablet formulation for oral administration in humans for the controlled release of ciprofloxacin in the stomach or upper part of the small intestine comprising a pharmaceutically effective amount of ciprofloxacin, about 0.2% to about 0.5% sodium alginate, about 0.5 to about 2.0% xanthan gum, about 10.0% to about 25% sodium

bicarbonate, and about 5.0% to about 20% cross-linked polyvinyl-pyrrolidone, said percentages being w/w of the composition, wherein the weight ratio of sodium alginate to xanthan gum is between about 1:1 to about 1:10, said ingredients present in said relative proportions in a single layer.

16. The formulation of claim 15 comprising 69.9% ciprofloxacin base, 0.34% sodium alginate, 1.03% xanthan gum, 13.7% sodium bicarbonate, 12.1% cross-linked polyvinylpyrrolidone, and optionally other pharmaceutical excipients.

17. The formulation of claim 15 in the form of a tablet.

18. A once daily tablet formulation for oral administration in humans for the controlled release of ciprofloxacin in the stomach or upper part of the small intestine comprising a pharmaceutically effective amount of ciprofloxacin, about 0.2% to about 0.5% sodium alginate, about 0.5 to about 2.0% xanthan gum, about 10.0% to about 25% sodium bicarbonate, and about 5.0% to about 20% cross-linked polyvinyl-pyrrolidone, said percentages being w/w of the composition, wherein the weight ratio of sodium alginate to xanthan gum is between about 1:1 to about 1:10.

19. The formulation of claim 18 comprising 69.9% ciprofloxacin base, 0.34% sodium alginate, 1.03% xanthan gum, 13.7% sodium

bicarbonate, 12.1% cross-linked polyvinylpyrrolidone, and optionally other pharmaceutical excipients.

20. The formulation of claim 18 in the form of a tablet.

21. A sustained release formulation comprising ciprofloxacin which releases more than 50% of the drug in less than 4 hours and releases more than 60% of the drug in less than 8 hours.

22. A sustained release formulation which releases more than 50% of the drug within about 2-4 hours and releases more than 60% of the drug within about 4-8 hours.

23. The formulation of claim 22, suitable for once-a-day profile.

24. The formulation of claim 23 in the form of a tablet or a capsule.

25. The formulation of claim 24 in the form of a tablet which is coated with a pharmaceutically acceptable excipient.

26. A sustained release formulation comprising 100-1000 mg of ciprofloxacin and pharmaceutically acceptable excipients, wherein the total weight of the dosage unit is less than 2000 mg.

27. The formulation of claim 26 wherein the pharmaceutically acceptable excipients comprises a viscolyzing agent and/or a gelling agent, a gas generating component, and a swelling agent.

28. The formulation of claim 27, which comprises from about 0.1% to about 8.0% of a viscolyzing agent and/or a gelling agent, about 5.0% to about 15% of a gas generating agent, and about 3.0% to about 15% of a swelling agent, said percentages being w/w of the composition.

29. The formulation of claim 28, which comprises from about 0.2% to about 5.0% of a viscolyzing agent and/or a gelling agent, about 5.0% to about 15% of a gas generating agent, and about 5.0% to about 15% of a swelling agent, said percentages being w/w of the composition.

30. The formulation of claim 29, wherein the viscolyzing agent is either xanthan gum or hydroxypropyl methylcellulose (methocel) and the gelling agent is sodium alginate.

31. The formulation of claim 30, wherein both the viscolyzing agent and sodium alginate are used.

32. The formulation of claim 31, wherein the viscolyzing agent is xanthan gum.

33. The formulation of claim 28, wherein the gas generating agent is selected from the group consisting of sodium bicarbonate, calcium carbonate, sodium carbonate and mixtures thereof.

34. The formulation of claim 28, wherein the swelling agent is crosslinked polyvinylpyrrolidone.

35. The formulation of claim 26 which is suitable for once-a-day profile.

36. The formulation of claim 26 in the form of tablet or capsule.

37. The formulation of claim 26 in the form of a tablet which is coated with a pharmaceutically acceptable excipient.

38. A sustained release solid dosage form of ciprofloxacin which, when orally administered in humans under fed conditions, provides mean peak serum/plasma concentration, area under the serum/plasma concentration–time curve above minimum inhibitory concentrations and durations above minimum inhibitory serum/plasma concentrations, of not less than 70% when compared with respect to divided doses of equivalent amount of conventional immediate release ciprofloxacin solid dosage form.

39. The sustained release solid dosage form of claim 38 which, when orally administered in humans under fed conditions, provides a medicament serum/plasma concentration – time curve with an area under the curve, time zero to infinity, ranging from about 3.5 to about 30 μg-hours/ml.

40. The sustained release solid dosage form of claim 38 which, when orally administered in humans under fed conditions, provides a mean

peak serum/plasma concentration ranging from about 0.5 to about 4 μg/ml.

41. The sustained release solid dosage form of claim 38 which, when orally administered in humans under fed conditions, provides a medicament serum/plasma concentration - time curve with an area under the curve above a minimum inhibitory concentration of 0.1 μg/ml, ranging from about 3 to about 26 μg-hours/ml.

42. The sustained release solid dosage form of claim 38 which, when orally administered in humans under fed conditions, provides a medicament serum/plasma concentration – time curve with an area under the curve above a minimum inhibitory concentration of 0.25 μg/ml, ranging from about 2 to about 22 μg-hours/ml.

43. The sustained release solid dosage form of claim 38 which, when orally administered in humans under fed conditions, provides a medicament serum/plasma concentration – time curve with an area under the curve above a minimum inhibitory concentration of 0.5 μg/ml, ranging from about 1 to about 18 μg-hours/ml.

FIG. 1

LINEAR PLOT OF MEAN SERUM CIPROFLOXACIN CONCENTRATIONS VERSUS TIME IN HEALTHY MALE HUMAN SUBJECTS

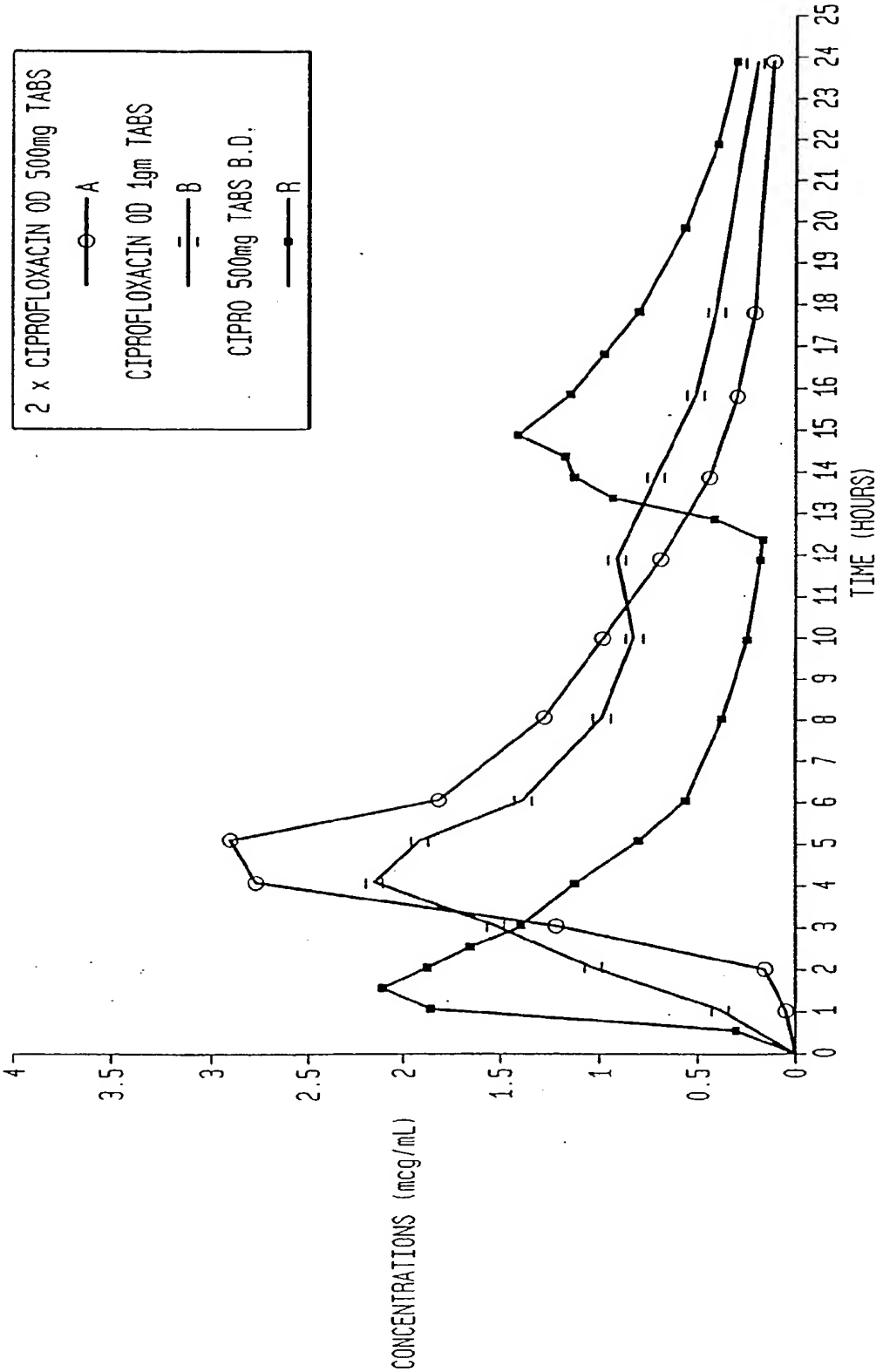


FIG. 2

LINEAR PLOT OF PLASMA CIPROFLOXACIN CONCENTRATIONS VERSUS TIME IN HEALTHY MALE HUMAN SUBJECTS (N=12)
(TEST FED VS. REFERENCE FED)

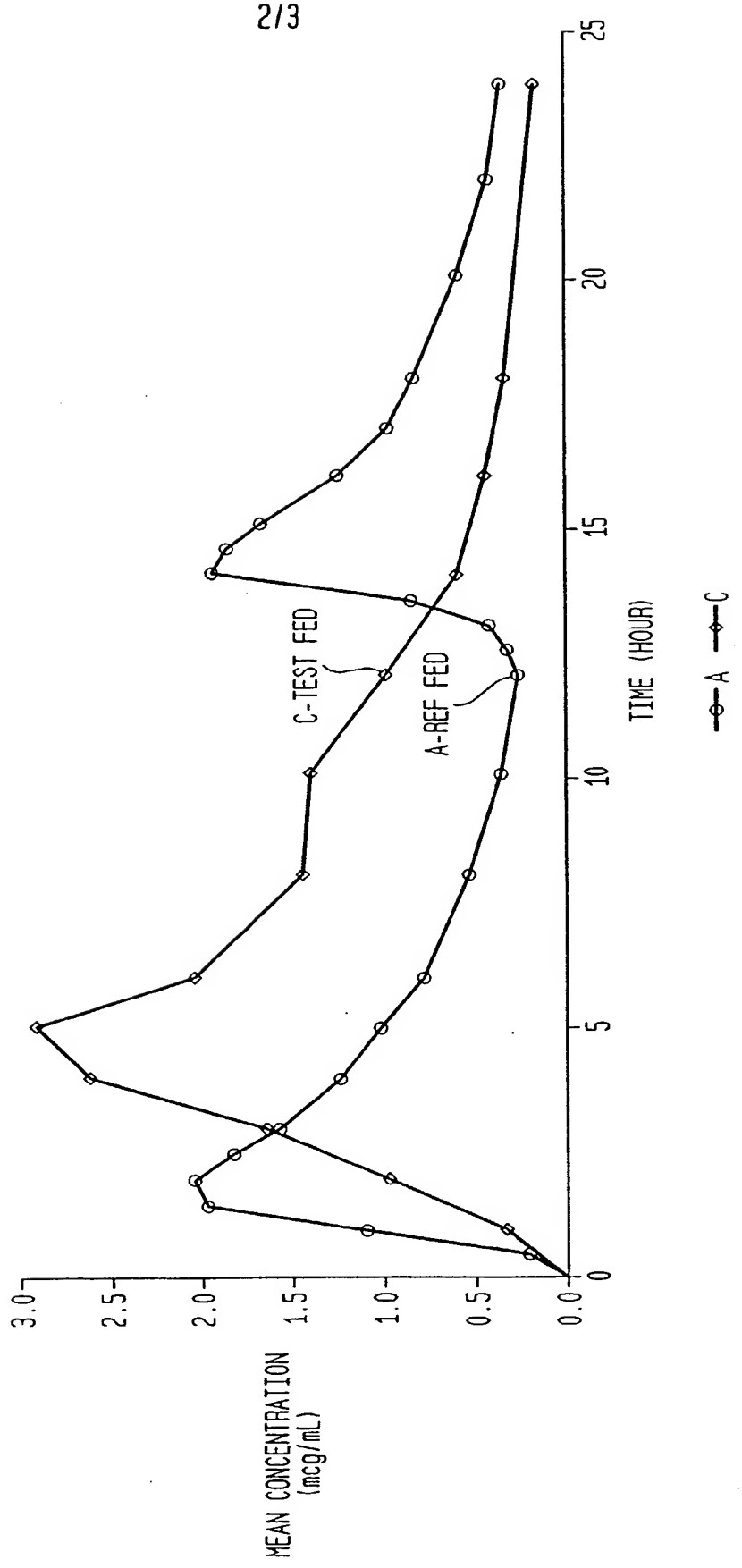
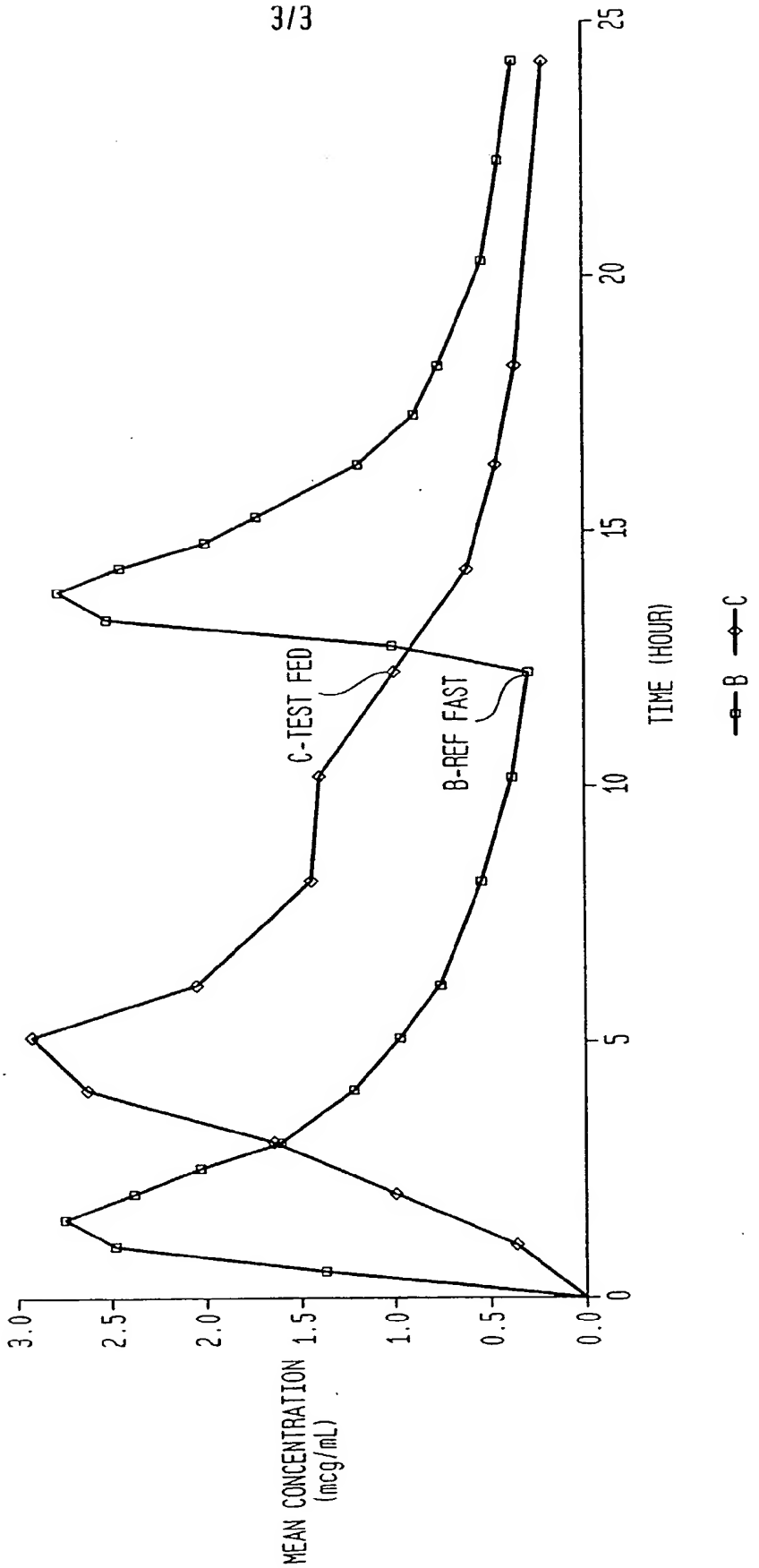


FIG. 3


MEAN CONCENTRATION (mcg/mL)
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0
5
10
15
20
25
TIME (HOUR)
C-TEST FED
B-REF FAST
B
C

INTERNATIONAL SEARCH REPORT

Ir ıal Application No
PCT/IB 01/00279

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/00 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI Section Ch, Week 199422 Derwent Publications Ltd., London, GB; Class A96, AN 1994-178692 XP002173158 & JP 06 024959 A (BAYER YAKUHIN KK), 1 February 1994 (1994-02-01) cited in the application abstract ---	1-43
X,P	WO 00 15198 A (RANBAXY) 23 March 2000 (2000-03-23) claims ---	1-43
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 August 2001	17/08/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 *epo nl*, Fax: (+31–70) 340–3016	Scarponi, U

1

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 292 518 A (E.H.KUHRTS) 8 March 1994 (1994-03-08) claims examples column 6, line 8 - line 38	1-43
A	EP 0 669 129 A (BAYER) 30 August 1995 (1995-08-30) cited in the application claims examples	1-43

INTERNATIONAL SEARCH REPORT

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Inte al Application No
PCT/IB 01/00279

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		CA 2030449 A	23-05-1991
EP 669129 A	30-08-1995	DE 4406424 A	31-08-1995
		CA 2143500 A	29-08-1995
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